PATENT COOPERATION TREATY

RECEIVED

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY FEB 2 0 2001

To:

NEEDLE & ROSENBERG PCT

Spratt,Gwendolyn D.
NEEDLE & ROSENBERG P.C.
127 Peachtree Street, N.E.
Suite 1200, The candler Building
Atlanta, GA 30303-1811
ETATS-UNIS D'AMERIQUE

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL PRELIMINARY EXAMINATION REPORT
(PCT Rule 71.1)

Date of mailing *(day/month/year)*	08.02.2001

Applicant's or agent's file reference	IMPORTANT NOTIFICATION
14014.0353/P	

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US99/27817	23/11/1999	25/11/1998

Applicant
THE GOVERNMENT OF THE UNITED STATES...ET AL

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

DOS/LMF/TMH
DOCKETED
By JMW Date 2/20/01
Reviewed _____
Name / Date

Name and mailing address of the IPEA/	Authorized officer
European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Danti, B Tel.+49 89 2399-8161

Form PCT/IPEA/416 (July 1992)

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	**FOR FURTHER ACTION**	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
14014.0353/P		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US99/27817	23/11/1999	25/11/1998
International Patent Classification (IPC) or national classification and IPC A61K39/395		
Applicant THE GOVERNMENT OF THE UNITED STATES...ET AL		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 8 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☒ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
21/06/2000	08.02.2001
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Wagner, R Telephone No. +49 89 2399 7357

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/US99/27817

I. Basis f th report

1. This report has been drawn on the basis of *(substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments (Rules 70.16 and 70.17).)*:
Description, pages:

1-31 as originally filed

Claims, No.:

1-43 as originally filed

Drawings, sheets:

1/4-4/4 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:

☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application.

☒ claims Nos. 1-30.

because:

☒ the said international application, or the said claims Nos. 1-30 regarding industrial applicability relate to the following subject matter which does not require an international preliminary examination (*specify*):
see separate sheet

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the said claims Nos. .

2. A meaningful international preliminary examination report cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the standard.

☐ the computer readable form has not been furnished or does not comply with the standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N) Yes: Claims 2,3,6,8,9,12,13,16,18,19,22-25,27-40,42,43

	No:	Claims	1,4,5,7,10,11,14,15,17,20,21,26,41
Inventive step (IS)	Yes:	Claims	
	No:	Claims	2,3,6,8,9,12,13,16,18,19,22-25,27-40,42,43
Industrial applicability (IA)	Yes:	Claims	31-43
	No:	Claims	

2. Citations and explanations
see separate sheet

VII. Certain defects in the international application

The following defects in the form or contents of the international application have been noted:
see separate sheet

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Claims 1-30 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

Re Item V

Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement.

1. Reference is made to the following documents:

D1: WO 95 29693 A (BRIGHAM AND WOMEN'S HOSPITAL) 9 November 1995 (1995-11-09)

D2: C. JORGENSEN ET AL.: 'Inhibition of human mucosal lymphocytes migration in rheumatoid synovium engrafted in SCID mice by antibodies against LFA-1 and alphaEbeta7 adhesion molecules.' ARTHRITIS AND RHEUMATISM, vol. 37, no. 9 suppl., September 1994 (1994-09), page S220 XP002129083 New York, NY, USA

D3: WO 98 06248 A (LEUKOSITE, INC.) 19 February 1998 (1998-02-19)

D4: R. O. Erhardt et al., Induction and Prevention of Colonic Inflammation in IL-2 deficient mice. J. Immunol., 1997, 158: 566-573.

The document D4 was not cited in the international search report but is cited in the application. A copy of the document is appended hereto.

2. As the priority claimed by the present application appears to be valid, the 2 documents cited as "P-X" in the international search report (Ludviksson et al.,

15.04.1999 and Kilshaw, August 1999) do not form part of the prior art.

3. For the assessment of the present claims 1-30 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

4. The subject-matter of claim 1 and dependent claims 4, 5, 7, 10 and 21 and claim 11 and dependent claims 14, 15, 17, 20, 26 is not novel (Article 33(2) PCT). D1 discloses that agents blocking the adhesion between T lymphocytes and E-cadherin expressing cells are useful for the treatment, i.e. reduction or prevention, (page 18, line 24) of autoimmune disease (page 8, third paragraph), which is characterised by inflammation. The treatment comprises the administration of an isolated peptide derived from the extracellular domain of E-cadherin which binds to $\alpha E\beta_7$ and inhibits the adhesion between an IEL and E-cadherin (page 9, first full paragraph). D1 discloses the treatment of ulcerative colitis, Crohn's, asthma, graft versus host disease by this method. D1 discloses also that the agent inhibiting the adhesion of T-lymphocytes is administered with other pharmaceutically active compounds (page 18, last paragraph).

5. The subject-matter of claims 6 and 16 is novel (Article 33(2) PCT) because D1 does not disclose the treatment of rheumatoid arthritis. It is however obvious to the skilled person in view of the disclosure of D2 showing that mucosal lymphocyte migration in rheumatoid synovium engrafted SCID mice can be inhibited by antibodies against $\alpha E\beta 7$ that rheumatoid arthritis, a typical autoimmune inflammatory disease, can also be treated (reduced or prevented - D2, page 18, line 24) by the antagonists to $\alpha E\beta 7$ disclosed in D1 or by the monoclonal antibody (HML-1) of D2. Therefore claims 6 and 16 do not involve an inventive step (Article 33(3) PCT).

6. Claims 8, 9, 18 and 19 are new (Article 33(2) PCT) but the obvious choice of allergy and graft rejection being 2 well-known autoimmune inflammatory

conditions involving mucosal cells and lymphocyte migration does not confer an inventive step (Article 33(3) PCT) on the treatment and prevention.

7. Claims 2, 3, 12 and 13 are novel (Article 33(2) PCT) because the prior art does not disclose the use of anti-αEβ7 antibodies for the treatment of inflammation. D1 discloses however that interaction between αEβ7 and E-cadherin can be inhibited by antibodies directed against E-cadherin and that a pharmaceutical composition containing said antibodies can be used for treating (reducing and preventing - page 18, line 24) mucosal inflammation. It is obvious to the skilled person that if an interaction between 2 ligands A and B can be inhibited by an antibody directed against ligand A the interaction can also be inhibited by an antibody against ligand B. This obvious deduction is reinforced by the fact that in D2 mucosal lymphocyte migration in rheumatoid synovium engrafted SCID mice can be inhibited by antibodies (HML-1) against αEβ7. Therefore the subject-matter of claims 2, 3 , 12 and 13 does not involve an inventive step (Article 33(3) PCT).

8. Claims 22-25 and 27-30 are new (Article 33(2) PCT) because the prior art does not disclose the precise combination therapies. As it is common practice to use combination therapy in the treatment of severe inflammatory diseases the choice of well-known (e.g Mab α4β7 as treatment of inflammatory disease, see D3, claim 47) anti-inflammatory compounds to be added to the αEβ7 antagonist does not add an inventive step (Article 33(3) PCT) to the treatment because said combinations do not appear to produce a surprising effect. Therefore the subject-matter of claims 22-25 and 27-30 does not involve an inventive step (Article 33(3) PCT).

9. Claims 31 to 40 are novel (Article 33(2) PCT) because the prior art does not disclose a method combining steps b) and c). D4 (table V) discloses that the administration of a substance (anti-IL-12) to TNP-KLH immunized IL-2 -/- mice induces a significant decrease of IFN-γ production. D2 discloses that in rheumatoid synovium engrafted SCID mice the antagonist of αEβ7 (monoclonal antibody HML-1) reduces the retention of injected lymphocytes. The method of claims 31 to 40 is therefore an apposition of 2 known methods which does not have a surprising effect. Therefore the subject-matter of claims 31 to 40 does not involve an inventive step (Article 33(3) PCT). The applicants attention is drawn to

the fact that in the regional or national phases some authorities will consider an invasive in-vivo test method which is carried out in humans as non-patentable. Humans fall within the scope of claims 31-33 and 35. This possible objection can be overcome by restricting the claims to non-human animals.

10. D1 discloses that agents blocking the adhesion between T lymphocytes and E-cadherin expressing cells are useful for the treatment, i.e. reduction or prevention, (page 18, line 24) of autoimmune disease (page 8, third paragraph), which is characterised by inflammation. The treatment comprises the administration of an isolated peptide derived from the extracellular domain of E-cadherin which binds to $\alpha E\beta_7$ and inhibits the adhesion between an IEL and E-cadherin (page 9, first full paragraph). D1 discloses also that the peptide, which is not an antibody is administered in a pharmaceutical composition with an appropriate pharmaceutically acceptable carrier (page 18, last paragraph). Therefore claim 41 is not new (Article 33(2) PCT).

11. Claims 42 and 43 are new (Article 33(2) PCT) because the prior art does not disclose compositions comprising αEβ7 antibodies with a pharmaceutically acceptable carrier. As the antibodies against αEβ7 are known (D1, page 24) and as use of a said antibodies as a medicament in monotherapy and in combination therapy is obvious (see sections V-7 and V-8) it is self-evident that the antibodies are formulated in a composition comprising a pharmaceutically acceptable carrier. Therefore the subject-matter of claims 42 and 43 does not involve an inventive step (Article 33(3) PCT).

Re Item VII

Certain defects in the international application

1. Contrary to the requirements of Rule 5.1(a)(ii) PCT, the relevant background art disclosed in the documents D1-D3 is not mentioned in the description, nor are these documents identified therein.

PATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

PCT

To:
NEEDLE & ROSENBERG P.C.
Attn. Spratt, Gwendolyn D.
127 Peachtree Street, N.E.
Suite 1200, The candler Building
Atlanta, GA 30303-1811
UNITED STATES OF AMERICA

RECEIVED
APR 2 8 2000
NEEDLE & ROSENBERG

NOTIFICATION OF TRANSMITTAL OF INTERNATIONAL SEARCH REPORT OR THE DECLARATION (PCT Rule 44.1)

Date of mailing *(day/month/year)*	20/04/2000
Applicant's or agent's file reference: 14014.0353/P	**FOR FURTHER ACTION** See paragraphs 1 and 4 below
International application No.: PCT/US 99/27817	International filing date *(day/month/year)*: 23/11/1999
Applicant: THE GOVERNMENT OF THE UNITED STATES...ET AL	

1. [X] The applicant is hereby notified that the International Search Report has been established and is transmitted herewith.

Filing of amendments and statement under Article 19:
The applicant is entitled, if he so wishes, to amend the claims of the International Application (see Rule 46):

When? The time limit for filing such amendments is normally 2 months from the date of transmittal of the International Search Report; however, for more details, see the notes on the accompanying sheet.

Where? Directly to the International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland
Fascimile No.: (41-22) 740.14.35

For more detailed instructions, see the notes on the accompanying sheet.

DOCS/LMW/TMH
DOCKETED
By: LMW Date: 4/28/00
Reviewed: LNF 4/30/00
Name/Date

2. [ ] The applicant is hereby notified that no International Search Report will be established and that the declaration under Article 17(2)(a) to that effect is transmitted herewith.

3. [ ] **With regard to the protest** against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

[ ] the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.

[ ] no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. **Further action(s):** The applicant is reminded of the following:

Shortly after **18 months** from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in Rules 90*bis*.1 and 90*bis*.3, respectively, before the completion of the technical preparations for international publication.

Within **19 months** from the priority date, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase until 30 months from the priority date (in some Offices even later).

Within **20 months** from the priority date, the applicant must perform the prescribed acts for entry into the national phase before all designated Offices which have not been elected in the demand or in a later election within 19 months from the priority date or could not be elected because they are not bound by Chapter II.

Name and mailing address of the International Searching Authority	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Nina Vercio

Form PCT/ISA/220 (July 1998)

NOTES TO FORM PCT/ISA/220

These Notes are intended to give the basic instructions concerning the filing of amendments under article 19. The Notes are based on the requirements of the Patent Cooperation Treaty, the Regulations and the Administrative Instructions under that Treaty. In case of discrepancy between these Notes and those requirements, the latter are applicable. For more detailed information, see also the PCT Applicant's Guide, a publication of WIPO.

In these Notes, "Article", "Rule", and "Section" refer to the provisions of the PCT, the PCT Regulations and the PCT Administrative Instructions respectively.

INSTRUCTIONS CONCERNING AMENDMENTS UNDER ARTICLE 19

The applicant has, after having received the international search report, one opportunity to amend the claims of the international application. It should however be emphasized that, since all parts of the international application (claims, description and drawings) may be amended during the international preliminary examination procedure, there is usually no need to file amendments of the claims under Article 19 except where, e.g. the applicant wants the latter to be published for the purposes of provisional protection or has another reason for amending the claims before international pbulication. Furthermore, it should be emphasized that provisional protection is available in some States only.

What parts of the international application may be amended?

Under Article 19, only the claims may be amended.

During the international phase, the claims may also be amended (or further amended) under Article 34 before the International Preliminary Examining Authority. The description and drawings may only be amended under Article 34 before the International Examining Authority.

Upon entry into the national phase, all parts of the international application may be amended under Article 28 or, where applicable, Article 41.

When? Within 2 months from the date of transmittal of the international search report or 16 months from the priority date, whichever time limit expires later. It should be noted, however, that the amendments will be considered as having been received on time if they are received by the International Bureau after the expiration of the applicable time limit but before the completion of the technical preparations for international publication (Rule 46.1).

Where not to file the amendments?

The amendments may only be filed with the International Bureau and not with the receiving Office or the International Searching Authority (Rule 46.2).

Where a demand for international preliminary examination has been/is filed, see below.

How? Either by cancelling one or more entire claims, by adding one or more new claims or by amending the text of one or more of the claims as filed.

A replacement sheet must be submitted for each sheet of the claims which, on account of an amendment or amendments, differs from the sheet originally filed.

All the claims appearing on a replacement sheet must be numbered in Arabic numerals. Where a claim is cancelled, no renumbering of the other claims is required. In all cases where claims are renumbered, they must be renumbered consecutively (Administrative Instructions, Section 205(b)).

The amendments must be made in the language in which the international application is to be published.

What documents must/may accompany the amendments?

Letter (Section 205(b)):

The amendments must be submitted with a letter.

The letter will not be published with the international application and the amended claims. It should not be confused with the "Statement under Article 19(1)" (see below, under "Statement under Article 19(1)").

The letter must be in English or French, at the choice of the applicant. However, if th language of the international application is English, the letter must be in English; if th language of the international application is French, the letter must be in French.

The letter must indicate the differences between the claims as filed and the claims as amended. It must, in particular, indicate, in connection with each claim appearing in the international application (it being understood that identical indications concerning several claims may be grouped),whether

(i) the claim is unchanged;

(ii) the claim is cancelled;

(iii) the claim is new;

(iv) the claim replaces one or more claims as filed;

(v) the claim is the result of the division of a claim as filed.

The following examples illustrate the manner in which amendments must be explained in the accompanying letter:

1. [Where originally there were 48 claims and after amendment of some claims there are 51]:
"Claims 1 to 29, 31, 32, 34, 35, 37 to 48 replaced by amended claims bearing the same numbers; claims 30, 33 and 36 unchanged; new claims 49 to 51 added."

2. [Where originally there were 15 claims and after amendment of all claims there are 11]:
"Claims 1 to 15 replaced by amended claims 1 to 11."

3. [Where originally there were 14 claims and the amendments consist in cancelling some claims and in adding new claims]:
"Claims 1 to 6 and 14 unchanged; claims 7 to 13 cancelled; new claims 15, 16 and 17 added." or
"Claims 7 to 13 cancelled; new claims 15, 16 and 17 added; all other claims unchanged."

4. [Where various kinds of amendments are made]:
"Claims 1-10 unchanged; claims 11 to 13, 18 and 19 cancelled; claims 14, 15 and 16 replaced by amended claim 14; claim 17 subdivided into amended claims 15, 16 and 17; new claims 20 and 21 added."

"Statement under article 19(1)" (Rule 46.4)

The amendments may be accompanied by a statement explaining the amendments and indicating any impact that such amendments might have on the description and the drawings (which cannot be amended under Article 19(1)).

The statement will be published with the international application and the amended claims.

It must be in the language in which the international appplication is to be published.

It must be brief, not exceeding 500 words if in English or if translated into English.

It should not be confused with and does not replace the letter indicating the differences between the claims as filed and as amended. It must be filed on a separate sheet and must be identified as such by a heading, preferably by using the words "Statement under Article 19(1)."

It may not contain any disparaging comments on the international search report or the relevance of citations contained in that report. Reference to citations, relevant to a given claim, contained in the international search report may be made only in connection with an amendment of that claim.

Consequence if a demand for international preliminary examination has already been filed

If, at the time of filing any amendments under Article 19, a demand for international preliminary examination has already been submitted, the applicant must preferably, at the same time of filing the amendments with the International Bureau, also file a copy of such amendments with the International Preliminary Examining Authority (see Rule 62.2(a), first sentence).

Consequence with regard to translation of the international application for entry into the national phase

The applicant's attention is drawn to the fact that, where upon entry into the national phase, a translation of the claims as amended under Article 19 may have to be furnished to the designated/elected Offices, instead of, or in addition to, the translation of the claims as filed.

For further details on the requirements of each designated/elected Office, see Volume II of the PCT Applicant's Guide.

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	**FOR FURTHER ACTION** see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
14014.0353/P		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/US 99/ 27817	23/11/1999	25/11/1998
Applicant		
THE GOVERNMENT OF THE UNITED STATES...ET AL		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 7 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

   a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   [ ] the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

   b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

   [ ] contained in the international application in written form.

   [ ] filed together with the international application in computer readable form.

   [ ] furnished subsequently to this Authority in written form.

   [ ] furnished subsequently to this Authority in computer readble form.

   [ ] the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   [ ] the statement that the information recorded in computer readable form is identical to the written sequence listing has be n furnished

2. [X] **Certain claims were found unsearchable** (See Box I).

3. [ ] **Unity of invention is lacking** (see Box II).

4. With regard to the **title,**

   [ ] the text is approved as submitted by the applicant.

   [X] the text has been established by this Authority to read as follows:

   ANTAGONISTS OF THE ALPHA E BETA 7 INTEGRIN AS THERAPEUTIC AGENTS FOR INFLAMMATORY DISEASES

5. With regard to the **abstract,**

   [X] the text is approved as submitted by the applicant.

   [ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from th date of mailing of this international search report, submit comments to this Authority.

6. Th figure of the **drawing** to be published with th abstract is Figure No. _____

   [ ] as suggested by th applicant.

   [ ] because the applicant failed to suggest a figure.

   [ ] because this figure better charact riz s th inv ntion.

   [X] Non of th figures.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 99/27817

B x I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Remark: Although claimS 1-30 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

B x II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International Application No
P[redacted]S 99/27817

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K39/395 G01N33/53 A61P1/04 A61P11/06 A61P19/02
A61P37/08 A61P37/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 95 22610 A (BRIGHAM AND WOMEN'S HOSPITAL) 24 August 1995 (1995-08-24) the whole document ---	1-20,31, 35,36, 41-43
X	WO 97 25423 A (ICOS CORPORATION) 17 July 1997 (1997-07-17) example 6 claims ---	1,4,6,7, 11,14, 16,17, 41,42
X	WO 95 29693 A (BRIGHAM AND WOMEN'S HOSPITAL) 9 November 1995 (1995-11-09) the whole document --- -/--	1,2, 4-12, 14-20, 41,42

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
13 April 2000	20/04/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Nooij, F

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Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	C. JORGENSEN ET AL.: "Inhibition of human mucosal lymphocytes migration in rheumatoid synovium engrafted in SCID mice by antibodies against LFA-1 and alphaEbeta7 adhesion molecules." ARTHRITIS AND RHEUMATISM, vol. 37, no. 9 suppl., September 1994 (1994-09), page S220 XP002129083 New York, NY, USA abstract 367 ---	1-3,6,7, 11-13, 16,17, 31,35, 36,42
X	C. JORGENSEN ET AL.: "Overexpression of integrin alphaEbeta7 on synovial fluid lymphocytes in rheumatoid arthritis and its regulation by sulfasalazine, sulfapyridine, 5-ASA and methotrexate." ARTHRITIS AND RHEUMATISM, vol. 37, no. 9 suppl., September 1994 (1994-09), page S255 XP000867268 New York, NY, USA abstract 575 ---	1,6,7, 11,16, 17,31, 35,41
X	M. PANG ET AL.: "Up-regulation of alphaEbeta7, a novel integrin adhesion molecule, on T cells from systemic lupus erythematosus patients with specific epithelial involvement." ARTHRITIS AND RHEUMATISM, vol. 41, no. 8, August 1998 (1998-08), pages 1456-1463, XP000867228 New York, NY, USA abstract page 1457, left-hand column, line 6 - line 16 page 1460, left-hand column, line 6 -right-hand column, line 15 figure 4 ---	1-3,7, 11-13, 17,31, 35,41-43
X	E. ROSTAPSHOVA ET AL.: "Integrin-mediated interactions influence the tissue specificity of CD8+ cytolytic T lymphocytes." EUROPEAN JOURNAL OF IMMUNOLOGY, vol. 28, no. 10, October 1998 (1998-10), pages 3031-3039, XP000867236 Weinheim, Germany abstract discussion figure 5 --- -/--	1-3, 9-13,19, 20

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	G. HADLEY ET AL.: "The epithelial cell-specific integrin, CD103 (alphaE integrin), defines a novel subset of alloreactive CD8+ CTL." THE JOURNAL OF IMMUNOLOGY, vol. 159, no. 8, 15 October 1997 (1997-10-15), pages 3748-3756, XP002129084 Baltimore, MD, USA abstract discussion	1-3, 9-13,19, 20
X	G. RUSSELL ET AL.: "Distinct structural and functional epitopes of the alphaEbeta7 integrin." EUROPEAN JOURNAL OF IMMUNOLOGY, vol. 24, 1994, pages 2832-2841, XP000672907 Weinheim, Germany abstract page 2833, left-hand column, line 13 - line 36 page 2839, left-hand column, line 15 -right-hand column, line 21 figure 7 page 2840, left-hand column, line 51 - line 54	1-4, 11-14
X	DATABASE WPI Week 9503 Derwent Publications Ltd., London, GB; AN 1995-018280 XP002129087 & JP 06 303990 A (KANEBO LTD.), 1 November 1994 (1994-11-01) abstract	1-3, 11-13
A	D. ALBERT ET AL.: "Gastrointestinal inflammatory disease in SIV-smmPBj-infected Macaca nemestrina is E-selectin independent yet characterized by recruitment of nondividing (KI-67), mucosal-specific (alphaEbeta7+) lymphocytes." JOURNAL OF MEDICAL PRIMATOLOGY, vol. 23, no. 4, June 1994 (1994-06), page 241 XP000867225 Copenhagen, Denmark abstract 30	1,4,11, 14

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
A	D. ELEWAUT ET AL.: "Enrichment of T cells carrying beta7 integrins in inflamed synovial tissue from patients with early spondyloarthropathy, compared to rheumatoid arthritis." JOURNAL OF RHEUMATOLOGY, vol. 25, no. 10, October 1998 (1998-10), pages 1932-1937, XP000867226 Toronto, Canada abstract discussion	1-3,6,7, 11-13, 16,17, 21-23, 25-28, 30,41-43
A	WO 98 06248 A (LEUKOSITE, INC.) 19 February 1998 (1998-02-19) the whole document	21-23, 25-28, 30,43
A	D. ANDREW ET AL.: "Distribution of alpha4beta7 and alphaEbeta7 integrins on thymocytes, intestinal epithelial lymphocytes and peripheral lymphocytes." EUROPEAN JOURNAL OF IMMUNOLOGY, vol. 26, no. 4, April 1996 (1996-04), pages 897-905, XP000867271 Weinheim, Germany the whole document	1-43
A	M. BAUMGART ET AL.: "Increase in the expression of alphaEbeta7, characteristic of intestinal intraepithelial lymphocytes, on T cells in the lung epithelium of patients with interstitial lung diseases and in synovial fluid of patients with rheumatic diseases." IMMUNOBIOLOGY, vol. 196, no. 4, December 1996 (1996-12), pages 415-424, XP000867231 Stuttgart, Germany discussion	1-43
A	C. ELANGBAM ET AL.: "Cell adhesion molecules-Update." VETERINARY PATHOLOGY, vol. 34, no. 1, January 1997 (1997-01), pages 61-73, XP000867246 Basel, Switzerland table 1 page 64, right-hand column, line 10 - line 32	1-43

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 99/27817

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
A	K. CEPEK ET AL.: "Integrin alphaEbeta7 mediates adhesion of T lymphocytes to epithelial cells." THE JOURNAL OF IMMUNOLOGY, vol. 150, no. 8 part 1, 15 April 1993 (1993-04-15), pages 3459-3470, XP002129085 Baltimore, MD, USA abstract discussion ---	1-43
P,X	B. LUDVIKSSON ET AL.: "Administration of mAb against alphaEbeta7 prevents and ameliorates immunization-induced colitis in IL-2-/- mice." THE JOURNAL OF IMMUNOLOGY, vol. 162, no. 8, 15 April 1999 (1999-04-15), pages 4975-4982, XP002129086 Baltimore, MD, USA the whole document ---	1-4, 11-14, 21-23, 25-28, 30-40, 42,43
P,X	P. KILSHAW: "AlphaEbeta7." MOLECULAR PATHOLOGY, vol. 52, no. 4, August 1999 (1999-08), pages 203-207, XP000867245 London, GB page 205, right-hand column, line 16 - line 34 -----	1-4, 11-14

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/US 99/27817

Patent document cited in search report	Publication date	Patent family member(s)	Publication dat
WO 9522610 A	24-08-1995	US 5594120 A	14-01-1997
		AU 1923095 A	04-09-1995
WO 9725423 A	17-07-1997	US 5922570 A	13-07-1999
		AU 1691297 A	01-08-1997
		US 5948891 A	07-09-1999
WO 9529693 A	09-11-1995	US 5610281 A	11-03-1997
		AU 2467695 A	29-11-1995
JP 6303990 A	01-11-1994	NONE	
WO 9806248 A	19-02-1998	AU 3972897 A	06-03-1998
		CN 1227607 A	01-09-1999
		EP 0918797 A	02-06-1999

PATENT COOPERATION TREATY

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PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

15

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
14014.0353/P		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US99/27817	23/11/1999	25/11/1998
International Patent Classification (IPC) or national classification and IPC A61K39/395		
Applicant THE GOVERNMENT OF THE UNITED STATES...ET AL		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 8 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☒ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
21/06/2000	08.02.2001
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Wagner, R Telephone No. +49 89 2399 7357

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/US99/27817

I. Basis f the r p rt

1. This report has been drawn on the basis of *(substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments (Rules 70.16 and 70.17).)*:
Description, pages:

1-31 as originally filed

Claims, No.:

1-43 as originally filed

Drawings, sheets:

1/4-4/4 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   - ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
   - ☐ the language of publication of the international application (under Rule 48.3(b)).
   - ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   - ☐ contained in the international application in written form.
   - ☐ filed together with the international application in computer readable form.
   - ☐ furnished subsequently to this Authority in written form.
   - ☐ furnished subsequently to this Authority in computer readable form.
   - ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
   - ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   - ☐ the description, pages:
   - ☐ the claims, Nos.:

☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application.

☒ claims Nos. 1-30.

because:

☒ the said international application, or the said claims Nos. 1-30 regarding industrial applicability relate to the following subject matter which does not require an international preliminary examination (*specify*):
see separate sheet

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the said claims Nos. .

2. A meaningful international preliminary examination report cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the standard.

☐ the computer readable form has not been furnished or does not comply with the standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and xplanations supporting such statement

1. Statement

Novelty (N) Yes: Claims 2,3,6,8,9,12,13,16,18,19,22-25,27-40,42,43

	No:	Claims	1,4,5,7,10,11,14,15,17,20,21,26,41
Inventive step (IS)	Yes:	Claims	
	No:	Claims	2,3,6,8,9,12,13,16,18,19,22-25,27-40,42,43
Industrial applicability (IA)	Yes:	Claims	31-43
	No:	Claims	

2. Citations and explanations
see separate sheet

VII. Certain defects in the international application

The following defects in the form or contents of the international application have been noted:
see separate sheet

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Claims 1-30 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

Re Item V

Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement.

1. Reference is made to the following documents:

D1: WO 95 29693 A (BRIGHAM AND WOMEN'S HOSPITAL) 9 November 1995 (1995-11-09)

D2: C. JORGENSEN ET AL.: 'Inhibition of human mucosal lymphocytes migration in rheumatoid synovium engrafted in SCID mice by antibodies against LFA-1 and alphaEbeta7 adhesion molecules.' ARTHRITIS AND RHEUMATISM, vol. 37, no. 9 suppl., September 1994 (1994-09), page S220 XP002129083 New York, NY, USA

D3: WO 98 06248 A (LEUKOSITE, INC.) 19 February 1998 (1998-02-19)

D4: R. O. Erhardt et al., Induction and Prevention of Colonic Inflammation in IL-2 deficient mice. J. Immunol., 1997, 158: 566-573.

The document D4 was not cited in the international search report but is cited in the application. A copy of the document is appended hereto.

2. As the priority claimed by the present application appears to be valid, the 2 documents cited as "P-X" in the international search report (Ludviksson et al.,

15.04.1999 and Kilshaw, August 1999) do not form part of the prior art.

3. For the assessment of the present claims 1-30 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

4. The subject-matter of claim 1 and dependent claims 4, 5, 7, 10 and 21 and claim 11 and dependent claims 14, 15, 17, 20, 26 is not novel (Article 33(2) PCT). D1 discloses that agents blocking the adhesion between T lymphocytes and E-cadherin expressing cells are useful for the treatment, i.e. reduction or prevention, (page 18, line 24) of autoimmune disease (page 8, third paragraph), which is characterised by inflammation. The treatment comprises the administration of an isolated peptide derived from the extracellular domain of E-cadherin which binds to $\alpha E\beta_7$ and inhibits the adhesion between an IEL and E-cadherin (page 9, first full paragraph). D1 discloses the treatment of ulcerative colitis, Crohn's, asthma, graft versus host disease by this method. D1 discloses also that the agent inhibiting the adhesion of T-lymphocytes is administered with other pharmaceutically active compounds (page 18, last paragraph).

5. The subject-matter of claims 6 and 16 is novel (Article 33(2) PCT) because D1 does not disclose the treatment of rheumatoid arthritis. It is however obvious to the skilled person in view of the disclosure of D2 showing that mucosal lymphocyte migration in rheumatoid synovium engrafted SCID mice can be inhibited by antibodies against $\alpha E\beta 7$ that rheumatoid arthritis, a typical autoimmune inflammatory disease, can also be treated (reduced or prevented - D2, page 18, line 24) by the antagonists to $\alpha E\beta 7$ disclosed in D1 or by the monoclonal antibody (HML-1) of D2. Therefore claims 6 and 16 do not involve an inventive step (Article 33(3) PCT).

6. Claims 8, 9, 18 and 19 are new (Article 33(2) PCT) but the obvious choice of allergy and graft rejection being 2 well-known autoimmune inflammatory

conditions involving mucosal cells and lymphocyte migration does not confer an inventive step (Article 33(3) PCT) on the treatment and prevention.

7. Claims 2, 3, 12 and 13 are novel (Article 33(2) PCT) because the prior art does not disclose the use of anti-αEβ7 antibodies for the treatment of inflammation. D1 discloses however that interaction between αEβ7 and E-cadherin can be inhibited by antibodies directed against E-cadherin and that a pharmaceutical composition containing said antibodies can be used for treating (reducing and preventing - page 18, line 24) mucosal inflammation. It is obvious to the skilled person that if an interaction between 2 ligands A and B can be inhibited by an antibody directed against ligand A the interaction can also be inhibited by an antibody against ligand B. This obvious deduction is reinforced by the fact that in D2 mucosal lymphocyte migration in rheumatoid synovium engrafted SCID mice can be inhibited by antibodies (HML-1) against αEβ7. Therefore the subject-matter of claims 2, 3 , 12 and 13 does not involve an inventive step (Article 33(3) PCT).

8. Claims 22-25 and 27-30 are new (Article 33(2) PCT) because the prior art does not disclose the precise combination therapies. As it is common practice to use combination therapy in the treatment of severe inflammatory diseases the choice of well-known (e.g Mab α4β7 as treatment of inflammatory disease, see D3, claim 47) anti-inflammatory compounds to be added to the αEβ7 antagonist does not add an inventive step (Article 33(3) PCT) to the treatment because said combinations do not appear to produce a surprising effect. Therefore the subject-matter of claims 22-25 and 27-30 does not involve an inventive step (Article 33(3) PCT).

9. Claims 31 to 40 are novel (Article 33(2) PCT) because the prior art does not disclose a method combining steps b) and c). D4 (table V) discloses that the administration of a substance (anti-IL-12) to TNP-KLH immunized IL-2 -/- mice induces a significant decrease of IFN-γ production. D2 discloses that in rheumatoid synovium engrafted SCID mice the antagonist of αEβ7 (monoclonal antibody HML-1) reduces the retention of injected lymphocytes. The method of claims 31 to 40 is therefore an apposition of 2 known methods which does not have a surprising effect. Therefore the subject-matter of claims 31 to 40 does not involve an inventive step (Article 33(3) PCT). The applicants attention is drawn to

the fact that in the regional or national phases some authorities will consider an invasive in-vivo test method which is carried out in humans as non-patentable. Humans fall within the scope of claims 31-33 and 35. This possible objection can be overcome by restricting the claims to non-human animals.

10. D1 discloses that agents blocking the adhesion between T lymphocytes and E-cadherin expressing cells are useful for the treatment, i.e. reduction or prevention, (page 18, line 24) of autoimmune disease (page 8, third paragraph), which is characterised by inflammation. The treatment comprises the administration of an isolated peptide derived from the extracellular domain of E-cadherin which binds to $\alpha E\beta_7$ and inhibits the adhesion between an IEL and E-cadherin (page 9, first full paragraph). D1 discloses also that the peptide, which is not an antibody is administered in a pharmaceutical composition with an appropriate pharmaceutically acceptable carrier (page 18, last paragraph). Therefore claim 41 is not new (Article 33(2) PCT).

11. Claims 42 and 43 are new (Article 33(2) PCT) because the prior art does not disclose compositions comprising $\alpha E\beta 7$ antibodies with a pharmaceutically acceptable carrier. As the antibodies against $\alpha E\beta 7$ are known (D1, page 24) and as use of a said antibodies as a medicament in monotherapy and in combination therapy is obvious (see sections V-7 and V-8) it is self-evident that the antibodies are formulated in a composition comprising a pharmaceutically acceptable carrier. Therefore the subject-matter of claims 42 and 43 does not involve an inventive step (Article 33(3) PCT).

Re Item VII

Certain defects in the international application

1. Contrary to the requirements of Rule 5.1(a)(ii) PCT, the relevant background art disclosed in the documents D1-D3 is not mentioned in the description, nor are these documents identified therein.